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POPULATION-GENETIC ASPECT OF SELECTED QUALITATIVE TRAITS DISTRIBUTION IN A SELECTED SAMPLE OF PERSONS WITH BREAST CANCER

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SUMMARY

Introduction: Breast cancer is the most common malignant tumor in women in general, around the world as a whole, which occurs when normal glandular cells of the breast change their properties and begin to grow uncontrollably, multiply and destroy the surrounding healthy tissue. Starting from the assumption that hereditary breast cancer has a multifactorial model, this article compares the distribution of selected qualitative characteristics in patients (experimental group) with the population-genetic structure of these characteristics from a healthy population (control group). **Aim:** Based on the experience of numerous researchers who studied certain monogenic and oligogenic qualitative traits in humans, the aim of this study was to determine the degree of genetic homozygosity using the homozygous recessive traits (HRT). **Methods:** This population-genetic study included two groups of respondents, experimental and control (80 in total). The study was conducted using a test for determining homozygous-recessive traits in humans (degree of homozygosity), the HRT-test, which includes a series of predominantly qualitative morphological and functional characteristics. The statistical significance of the differences between the obtained and expected values of recessive homozygotes was assessed using the Chi-square test. The expected values of recessive homozygotes were obtained using the Hardy-Weinberg formula: p2 + 2pq + q2aa = 1, which is valid when the population is in genetic equilibrium. **Results:** A statistically significant difference in the frequency of occurrence between the examined groups was determined for the following phenotypes: two flowers in the hair, soft hair, inability to bend the tongue, speech defect "R", absence of malleus on the phalanges of patients and healthy differ in approximately 25% of gene alleles. **Conclusion:** This finding suggests the possibility of association of appropriate gene alleles with the genetic susceptibility for breast cancer. As a cause of increased recessive homozygosity in patients with breast cancer, there is a genetic burden that could cause reduced resistance to environmental factors as the main triggers for the development of this type of cancer.

KEYWORDS: breast cancer; HRT-test; genetic homozygosity, allelic frequency.

INTRODUCTION

Cancer is a genetic disease. All tumors are the result of the accumulation of mutations and deregulation of proto-oncogenes and tumor suppressor genes, as well as genes involved in the control of cell growth, cell survival and DNA maintenance.[1]

Breast cancer is the most common malignant tumor in women in the world, which occurs when normal glandular cells of the breast change their properties and begin to grow uncontrollably, multiply and destroy the surrounding healthy tissue.

Breast cancer incidence and mortality rates have increased over the past three decades. Between 1990 and 2016, the incidence of breast cancer more than doubled in 60 of 102 countries (e.g., Afghanistan, the Philippines, Brazil, Argentina). The number of deaths doubled in many countries (e.g., Yemen, Paraguay, Libya, Saudi Arabia).[3] Current projections show that by 2030, the number of new diagnosed cases worldwide will reach 2.7 million per year, while the number of deaths will be 0.87 million.[4]

The majority of breast cancers occurs in the upper outer quadrant and the outgrowths of glandular tissue directed towards the axilla (armpit). Malignant breast tumors are most often of epithelial origin. They can arise from ductal epithelium (90%) or lobular epithelium (10%), both of which are divided into those that have not penetrated the basement membrane (non-infiltrating in situ) and those that have penetrated (infiltrating).[5]

One of the main risk factors is heredity, and the two genes responsible for hereditary breast cancer (discovered in 1994 and 1995) are called Breast Cancer 1 and Breast Cancer 2, or BRCA-1 and BRCA-2. Women who inherit mutated genes are at greater risk, according to some experts, up to 80%.[6]

It is estimated that approximately 1 in 300 women (0.33%) have the BRCA1 mutation. While around 4% of all breast cancer cases are attributed to BRCA1 mutations.[7]

In more than half of women, the disease appears by the age of fifty, and in some even in their thirties. Genes can be passed on by either parent and the children have a 50:50 chance of inheriting them.[8]

The risk group includes women with a family history of breast cancer (mother, sister), barren women and those who gave birth after the age of 35, women with prolonged menstrual activity (menstruation started before the age of 12 and menstruating for thirty or more years). Women who have already had breast surgery due to cancer have a 4 to 5 times higher risk of developing cancer in the other breast women with benign proliferative breast diseases and women who have had received impact to the breast (physical trauma).[9]

In study analyzes of the family at the cellular level, BRCA1 and BRCA2 have the properties of tumor suppressor genes, that is, genes that are not dominant but recessive.[10]

Recessiveness imply that the protective function of tumor suppressor genes exists if at least one member of the allelic pair is normal (so if heterozygosity exists), and it stops when both members are mutated or when one mutates and the other is deleted (so if heterozygosity is lost). In other words, the prerequisite for malignant cell transformation is the loss of heterozygosity of the tumor suppressor gene locus. Two additional tumor suppressor genes, p53 and PTEN, Ha-ras oncogene and estrogen receptor genes are related to breast cancer.[11]

In families with a high frequency of breast cancer, a higher frequency of ovarian, colon, prostate (in men) and other organ cancers was recorded.[12]

In order to examine the role of genetic factors in the cancer development, numerous population genetic and cytogenetic studies were conducted.[13-15]

AIM

- Analyze the frequency and distribution of selected phenotypic traits using the homozygous-recessive trait (HRT) test in humans in a selected sample of healthy individuals and individuals with breast cancer.
- To pre-diagnose the probability (risk estimate) of disease development in healthy women by analyzing homozygous recessive traits (HRT).
- Determining the degree of genetic homozygosity and variability in subjects of the experimental group compared to subjects of the control group.

The study will contribute to the expansion of knowledge in the field of examining the genetic basis of breast cancer in women in the Federation of Bosnia and Herzegovina, and better prevention by the HRO analysis.

Specific importance lies in the individual assessment of the breast cancer probability risk through HRT analysis.

MATERIALS AND METHODS

Many population geneticists base their research on determining the representation and distribution of racial traits in order to assess individual and group differences in relation to other characteristics.[16-24].

This anthroposcopic-qualitative study includes two groups of respondents.

Experimental group -The presence of HRT was examined in 40 female respondents suffering from breast cancer only from the territory of the Federation of Bosnia and Herzegovina. The inclusion criterion for the experimental group was confirmation of the diagnosis based on official medical records, PH findings. Persons who had other diagnoses related to malignant processes were not included in the experimental group.

Control group - Included 40 healthy female subjects, also only from the territory of the Federation of Bosnia and Herzegovina. The control group was obtained by random selection, where care was taken to ensure that there was no familial predisposition to the development of breast cancer.

All respondents give informed consent to participate in the study, while the applied methodology ensures the anonymity of data processing and publication. A morphophysiological approach was used to collect data. Each respondent was determined by direct observation and interview to have a phenotype variant of the researched traits.

During the study, the "HRT test" was used for selected 20 qualitative morphological and functional characteristics that are under the control of genetic factors and cover all regions of the human body: hair characteristics, facial characteristics, pronunciation,

tongue mobility, finger characteristics, hand characteristics, and finger mobility.

Statistical analysis

The paper analyzed possible genetic burdens caused by increased recessive homozygosity in the studied populations.

The statistical significance of the differences between the obtained and expected values of recessive homozygotes was assessed using the Chi-square test. The expected values of recessive homozygotes were obtained using the Hardy-Weinberg formula: p2 + 2pq + q2aa = 1, which is valid when the population is in genetic equilibrium.

RESULTS

Table 1: Comparative analysis of clinical, laboratory and anthropometric parameters between control and experimental groups.

Variable	Control group (n=40)	Experimental group (n=40)	p
Rh+	32 (80%)	34 (85%)	0.556
Birth	32 (80%)	33 (82.5%)	0.775
Pregnancy termination	11 (27.5%)	13 (32.5%)	0.626
Breastfeeding	28 (70%)	26 (65%)	0.633
Smoking	14 (35%)	15 (37.5%)	0.816
Alcohol use	4 (10%)	1 (2.5%)	0.179
Contraceptives	6 (15%)	8 (20%)	0.556
Presence of benign disease	7 (17.5%)	3 (7.5%)	0.155
Positive family history	11 (27.5%)	15 (37.5%)	0.340
Presence of metastasis	0 (0%)	21 (52.5%)	<0.001
Regular control examinations	23 (57.5%)	40 (100%)	<0.001
Blood type (A/B/AB/0)	25 (62.5%) /3 (7.5%) /3 (7.5%) / 9 (22.5%)	22 (55%) / 6 (15%) / 2 (5%) / 10 (25%)	-
Age of diagnosis (<30 yrs. / 31-40 yrs. / 41-50 yrs. / >50 yrs.	-	0 (0%) / 4 (10%) / 10 (25%) / 26 (65%)	-
Body Mass Index	24.84±3.39	25.32±2.75	0.494

Table 1 present the analysis of clinical, laboratory and anthropometric parameters between the control and experimental groups. Of all the examined clinical, laboratory and anthropometric parameters, differences in the frequency of occurrence between the experimental and control groups were noted in the presence of metastases ($p<0.001$) and in the practice of conducting regular control examinations ($p<0.001$).

Table 2: Examined HRT, their presence and results of the Chi-square test in two groups.

Characteristic	Experimental group			Control group			p
	N	%	q	N	%	q	
Flat scalp	25	62.5	7.90	17	42.5	6,52	0.073
Two flowers in hair	7	17.5	4.18	0	0	0	0.006
Soft hair	34	85	9.22	25	62.5	7.90	0.022
Straight hair	27	67.5	8.21	22	55	7.42	0.251
Tied earlobe	16	42.5	6.52	24	60	7.74	0.117
Ear without Darwin's lump	24	60	7.74	21	52.5	7.24	0.499
Thin lips	27	67.5	8.21	26	65	8.06	0.813
Receded teeth	7	17.5	4.18	3	7.5	2.74	0.176
Retracted chin	4	10	3.16	3	7.5	2.74	0.500
Absence of mallets	24	60	7.74	24	60	7.74	1.0
Narrow nostrils	23	57.5	7.58	22	55	7.42	0.822
Inability to bend the tongue longitudinally	16	40	6.32	13	32.5	5.70	0.485
Inability to bend the tongue backwards	11	27.5	5.24	4	10	3.16	0.045
Speech impediment “R”	8	20	4.47	1	2.5	1.58	0.014
Right thumb over left	20	50	7.07	23	57.5	7.58	0.501
Mobility of the distal part of the thumb	8	20	4.47	6	15	3.87	0.556
Ability to reach the forearm with the thumb	3	7.5	2.74	9	22.5	4.74	0.060
Arm crossing (R-phenotype)	19	47.5	6.89	22	55	7.42	0.502
Absence of mallets on the phalanges	26	65	8.06	34	85	9.22	0.039
Three tendons at the root of the hand	32	80	8.94	28	70	8.37	0.302

Table 2 present the absolute and relative frequency of 20 analyzed homozygous recessive traits (HRT) in persons with breast cancer and the control group.

A statistically significant difference in the frequency of occurrence between the examined groups was determined for the following phenotypes: two flowers in the hair, soft hair, inability to bend the tongue, speech defect "R", absence of malleus on the phalanges.

The determined differences in the frequency of occurrence of the other analyzed traits between the examined groups were not statistically significant.

DISCUSSION

Recorded differences in the frequency of genotypes indicate that the balance is disturbed at the level of individual genotypes in the part of the population affected by breast cancer, whereby recessive homozygotes become more common in comparison with heterozygotes.

Based on these data and data on the frequency of corresponding recessive alleles, it can be concluded that the genetic structure of breast cancer patients differs from the genetic structure of the general population to which they belong.

The hypothesis that genetic burdens, caused by increased recessive homozygosity, in patients with breast cancer could be the cause of reduced resistance to external factors responsible for the onset of this disease, received significant support from these studies.

The results of this study show similarities with the results on some other diseases, such as tumors of the urinary system, tumors of other locations, endemic nephropathy and spinal dysraphism.[25-26]

Genetic burdens essentially reduce the degree of adaptation of individuals of the population, and it could result in breast cancer patients not only having a reduced resistance to this, but perhaps also to other diseases, e.g., tumors of the urinary tract[21-23] and tumors of other locations. The results obtained from these studies impose the need for a more detailed analysis of the external factors that could cause the disruption of the genetic balance of the population affected by breast cancer.

The possibility of errors in the assessment of the analyzed morgological-physiological properties, the imperfection of the methodology itself for processing these data should also be taken into account.

CONCLUSION

Based on all presented, the following can be concluded.

- Five of the twenty analyzed recessive phenotypes show a statistically significantly higher frequency in breast cancer patients compared to healthy individuals (control group).
- Bearing in mind that the analyzed qualitative traits were randomly chosen, as well as the fact that they are under relatively simple genetic control, it can be assumed that the genetic structure of diseased and healthy patients differ in approximately 25% of gene alleles.

This finding suggests the possibility of association of the corresponding gene alleles with the genetic basis for breast cancer. As a cause of increased recessive homozygosity in patients with breast cancer, there is a genetic burden that could cause reduced resistance to environmental factors as the main triggers for the development of this type of cancer.

Although the number of respondents in this study is relatively low, the results obtained in this, as well as in similar studies[27], show a clear population-genetic difference in the degree of genetic homozygosity and variability compared to healthy subjects.

These studies should be expanded, both with the number of respondents and by introducing new methods.

So, the use of the HRT test in the future can confirm its applicability in determining genotypes that are associated with different diseases.

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